131. The modified wild-type human TSH of Claim 106, further modified so that said modified wild-type human TSH has complete amino acid sequence homology with the corresponding wild-type human TSH in said α-subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

132. A modified wild-type human thyroid stimulating hormone (TSH) having increased TSH activity compared to wild-type human TSH comprising an α-subunit and a β-subunit, said β-subunit comprising a basic amino acid in the β-subunit in at least one position selected from the group consisting of positions 58, 63, and 69.

133. The modified wild-type human TSH of Claim 132, wherein the basic amino acids of the β-subunit are at positions 58, 63, and 69.

134. The modified wild-type human TSH of Claim 132, wherein a basic amino acid of the β-subunit is at position 58.

135. The modified wild-type human TSH of Claim 132, wherein a basic amino acid of the β-subunit is at position 63.

136. The modified wild-type human TSH of Claim 132, wherein a basic amino acid of the β-subunit is at position 69.

137. The modified wild-type human TSH of Claim 132, wherein the basic amino acids are selected from the group consisting of lysine and arginine.

138. A nucleic acid encoding the modified wild-type human thyroid stimulating hormone (TSH) β-subunit of Claim 132.

139. A vector comprising the nucleic acid of Claim 138, wherein the vector is suitable for expressing the nucleic acid.

140. A host cell comprising the vector of Claim 139, wherein the host cell is suitable for expressing the nucleic acid.

REMARKS

Applicant wishes to thank Examiner Spector for the courtesy extended to their representative, Nancy W. Vensko, and colleagues, on December 19, 2000. The Interview Summary Form PTOL-413 summarizes the discussions held at the personal interview. The present response to the outstanding Office Action includes the substance of the Examiner Interview.

I. Disposition Of Claims

By this amendment, Applicant has canceled all pending claims, that is, Claims 1-80, prior to further examination of this application, in order to protect a commercial embodiment, and, thus, for reasons unrelated to patentability. Claims 81-140 have been added. Thus, Claims 81-140 are presented for examination. Support for the amendment is found throughout the specification, as discussed below. No new matter is added. Reexamination and reconsideration of the application, as amended, are respectfully requested.

II. Review of Invention

The present application was published as Szkudlinski et al., Nature Biotechnology, 14:1257 (October 1996) (attached). Additionally, R. Ruddon published an analysis of this research in R. Ruddon, Nature Biotechnology 14:1224 (October 1996) (attached). Dr. Ruddon described the presently claimed invention. He said that, up until now, there have been no reports indicating a way to produce a TSH with both increased receptor binding activity and in vivo bioactivity. He said that Szkudlinski et al. have generated by site-directed mutagenesis a series of "superactive analogs" of human TSH. The design of these analogs was based on the observation that the common α-subunit, though highly conserved, differs among species in a domain containing amino acid residues 11 to 21 forming the L1 loop. On the basis of previous observations that the 11-21 region is not involved in α-β contact sites (from the crystal structure and antibody reactivity) and that the L1 loop appears to be involved in receptor binding, Szkudlinski et al. hypothesized that by substituting basic amino acids for neutral ones in this region, a weak, hydrogen bond-type, hormone-receptor interaction would be replaced by a stronger electrostatic interaction with acidic amino acids of the receptor. Not only were receptor binding affinity and cyclic AMP formation increased in cell culture models for human TSH, but also in vivo potency and efficacy were increased in a mouse model for TSH-induced secretion of thyroid hormone. In the patent specification, Szkudlinski et al. extended this research to a domain containing amino acid residues 58 to 69 forming the L3 loop of the β-subunit. The results

illustrated in Figures 2g, 2h, and 2i show that by substituting basic amino acids for neutral ones in this region, similarly, not only were receptor binding affinity and cyclic AMP formation increased in cell culture models for human TSH, but also in vivo potency and efficacy were increased in the mouse model for TSH-induced secretion of thyroid hormone.

III. Formal Matters Regarding Benefit Of Priority

This application claims the benefit of priority of an earlier application and thus is amended to refer to the prior application in the first sentence of the patent specification per 37 CRF 1.78.

IV. Matters Analogous To Certificate Of Correction

Whenever a mistake of a clerical or typographical nature or of minor character appears in a patent and a showing is made that such mistake occurred in good faith, the patent office may issue a certificate of correction, if the correction does not involve such changes as would constitute new matter or would require reexamination. Here is an analogous situation in which such mistake has occurred and a correction would not involve such changes. Thus, the term "modified wild-type TSH" in the claims is clear, in light of the definition given at p. 7 (and p. 22) in the patent specification, because the basis for comparison is "the corresponding wild-type human TSH." Applicant gratefully acknowledges this and other corrections suggested by the Examiner.

V. Human TSH Muteins Having Basic Amino Acid Substitutions In That Loop

The Examiner rejected Claims 74-78 under 35 USC 112/1, on the allegation that the specification, while providing an adequate written description and enablement of human TSH muteins having basic amino acid substitutions at α-subunit positions 11, 13, 14,16, 17, and 20 having increased TSH activity, or having a basic amino acid substitution at position 69 of the β-subunit and increased TSH activity, does not reasonably provide written description or enablement for any other substitutions, either in TSH or in others of the glycoprotein hormones, which result in increased hormone activity. Applicant has canceled these claims, prior to further examination of this

application, in order to protect a commercial embodiment, and, thus, for reasons unrelated to patentability.

By comparison, the pending claims are directed to a modified wild-type human TSH having increased TSH activity compared to wild-type human TSH comprising an α-subunit and a β-subunit, the α-subunit comprising a basic amino acid substitution at positions selected from the group consisting of positions 11, 13, 14,16, 17, and 20 (in the L1 loop), or the β-subunit comprising a basic amino acid substitution at positions selected from the group consisting of positions 58, 63, and 69 (in the L3 loop). Thus, with the exception of β-subunit positions 58 and 63, the Patent Office is in agreement that such claims meet the requirements of 35 USC 112/1.

As for the disputed positions, the results illustrated in Figures 2g, 2h, and 2i show that by substituting basic amino acids for neutral ones in a domain containing amino acid residues 58, 63, and 69 forming the L3 loop of the β-subunit, not only were receptor binding affinity and cyclic AMP formation increased in cell culture models for human TSH, but also in vivo potency and efficacy were increased in the mouse model for TSH-induced secretion of thyroid hormone. Thus, all pending claims meet the specification requirements of Title 35.

VI. Campbell et al., WO91/16922 Describe hCG Analogs

The Examiner rejected the claims under 35 USC 102(b) as being anticipated by Campbell et al. or under 35 USC 103 as being unpatentable over Campbell et al. Campbell et al. describe modified human chorionic gonadotropin (hCG) α,β-heterodimeric polypeptides comprising an α-subunit and a β-subunit, in which the modified hCGs are different compared to native hCG, where the α- subunit can be naturally occurring and the β-subunit can be non-naturally occurring.

The law of anticipation requires that all elements of a claim be identically disclosed in a reference. Additionally, the law of obviousness requires that the invention as a whole would have readily occurred to one skilled in the art. Campbell et al.'s modified hCG α,β-heterodimeric polypeptides comprising an α-subunit and a β-subunit, in which the modified hCGs are different compared to native hCG, do not anticipate or make obvious the present invention.

To the contrary, Campbell et al. did not design any "superactive analogs" of human TSH based on the observation that the common α-subunit, though highly conserved, differs among species in a domain containing amino acid residues 11 to 21 forming the L1 loop. Campbell et al. did not make any mutations on the basis that the 11-21 region lacks involvement in α-β contact sites (from the crystal structure and antibody reactivity) or that the L1 loop appears to be involved in receptor binding. Campbell et al. did not appreciate that by substituting basic amino acids for neutral ones in this region, a weak, hydrogen bond-type, hormone-receptor interaction would be replaced by a stronger electrostatic interaction with acidic amino acids of the receptor. Neither did Campbell et al. extend this research to a domain containing amino acid residues 58 to 69 forming the L3 loop of the β-subunit. Campbell et al. did not test any superactive analogs for TSH activity by any receptor binding assay or cyclic AMP formation in cell culture models, nor for in vivo potency or efficacy in any animal model of TSH-induced secretion of thyroid hormone.

Rather, Campbell et al. describe modified human chorionic gonadotropin (hCG) α,β-heterodimeric polypeptides comprising an α-subunit and a β-subunit, in which the modified hCGs are different compared to native hCG. While Campbell et al. proposed to introduce mutations throughout the α-subunit (Table IX), these combine with hCG β-subunit to form modified hCGs and bind to LH receptors (Table XIV). Even if Campbell et al. combined the α-subunit with hCG/TSH β-subunit chimeras of Table III, the heterodimers would merely qualify as modified hCGs. This is because Campbell et al. proposed to substitute "TSH" amino acids for "hCG" amino acids throughout the hCG β-subunit (see Table III). Thus, the result would not qualify as a modified wild-type human TSH as defined at p. 7 (and p. 22) in Applicant's specification. Actually, Campbell et al. teach away from the present invention by expecting their hCG/TSH β-subunit chimeras (presumably in combination with an α-subunit) to be useful as TSH antagonists. At page 23, last ¶. By comparison, the modified hTSHs of the present invention possess increased TSH activity compared to wild-type hTSH, thus making them useful as TSH agonists. Consequently, not only is Campbell et al. insufficient in challenging the novelty of the present invention, but also, it teaches away, which is the very antithesis of obviousness.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 2/2/01

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